C3 D4 (e) selecting at least one vaccine composition that exceeds a predetermined level of said T cells' response for assessment in one or more human subjects.

C4 17. (Twice Amended) The method of Claim 11 wherein the monoclonal human T cells are $CD8^+$ T cells or $CD4^+$ T cells and the T cell epitope is a CD8 epitope or CD4 epitope.

C5 20. (Twice Amended) The method of Claim 11 wherein the human antigen presenting cells are autologous cells with the monoclonal T cells.

Please add new Claims 21 - 22 shown below.

C6 21. (New) The method of Claim 1, wherein the vaccine composition further comprises an immunostimulating complex.

22. (New) The method of Claim 1, wherein steps (a) and (b) are conducted simultaneously.

REMARKS

Applicant has corrected his copy of the previous Office Action, page 2, line 11, in accordance with the Examiner's Request, to read "Claims 1-9 and 11-20 are rejected."

The remainder of this response is set forth under separate headings.

Status of Claims

Claims 1-9 and 11-20 are currently pending in the application. Claims 2-3, 9, 12-16 and 18-19 are cancelled by this amendment. Claims 1, 4-8, 11, 17, and 20 have been amended. Claims 21-22 have been added.

Claim Amendment

Claim 1 has been amended to delete "one or more antigens" or "one or more nucleic acid molecules..." and to define the vaccine compositions used as those having a defined human T cell epitope or one or more nucleic acid molecules encoding one or more antigens which comprise said T cell epitope, and to specify that the T- cell response is a monoclonal human T cell response. Further, the antigen presenting cells in steps (a) and (b) are defined as human antigen presenting cells that are contacted with monoclonal human T cells having a T cell receptor specific for the defined human T cell epitope or defined peptide and known HLA allele for said T cell. Part (c) of Claim 1 has been amended to delete "whether" the "T cells respond" and to specify that the step includes determining the level of said T cells' response. Claim 11 has been similarly amended. Support for the amendment is found throughout the specification, and in particular in original Claims 2 and 3, and on page 4, lines 12-31. Further support is provided on page 10, lines 1-7, where it is stated that "preferably the T cells are specific for a particular epitope...," and that "in a particularly preferred embodiment, the T cells are human T cell clones." In part (d) of Claim 1 and Claim 11, assessing in animals has been deleted to emphasize the applicability of the method to human vaccine development.

Claims 4 and 5 have been amended to properly depend from Claim 1; to specify that the T cells are monoclonal human T cells, and that the T cell epitope is a CD8 epitope or a CD4 epitope, respectively. Support for this amendment is found on page 10, at lines 9-24. Claims 6-8 have been amended to properly depend from Claim 1. In Claim 7, the antigen presenting cells are specified as human. In Claims 7-8, the level of human T cell response to processed antigen is specified, in accordance with amended Claim 1. Claims 17 has been amended to properly depend from Claim 11, and to specify monoclonal human T cells and that the T cell epitope is a CD8 epitope or CD4 epitope. Claim 20 has been amended to properly depend from Claim 11 and to specify human antigen presenting cells.

New Claims 21-22 have been added. Support for new Claim 21 is provided at page 5, lines 14-15 and lines 19-20, wherein vaccines are described, the vaccines including "attenuated or killed pathogens, for example, ..." which are "administered in a suitable vector, such as a recombinant virus or bacterium or an immunostimulating complex."

Support for new Claim 22 is provided at page 9, lines 27-29, wherein it is described that "alternatively, the antigen presenting cells can be contacted with the vaccine composition and the T cells simultaneously, or within a relatively short time-interval."

Advantages of Applicant's Invention

Applicant believes that his invention, by permitting faster and more efficient screening of a panel of vaccine candidates with a particular epitope than screenings currently performed, represents a significant advance in vaccine development techniques. Applicant's claimed method generally requires less than 24 hours, while the assays required in the method of the prior art require immunogenicity protocols *in vivo* that require a long period of time to complete.

Applicant's claimed method is commercially viable and promises to be not only quicker, but more economical than the prior art methods. Further, the human T cell system utilized in Applicant's invention is more directly relevant to human *in vivo* immunogenicity than are traditional methods of vaccine testing. For example, a positive response in a mouse system may not apply to humans because mouse MHC presents peptide types different from that of human HLA.

The animal antigenicity studies are expensive and take a great deal of time, as described above. Usually several doses of experimental vaccine are administered at intervals of several weeks. In addition to the substantial cost for the purchasing and housing of animals for months at a time, there are at least several months of time expended before moving to the next step. Another disadvantage to prior art methods is the need to drastically limit the number of experimental vaccines to be tested in these *in vivo* assays, due to their expense. This financial restriction may result in not developing potentially useful vaccine constructs.

In contrast to traditional methods, Applicant's claimed method works *in vitro* with monoclonal human T cells specific for a defined human T cell epitope. Technology proposed by Applicant includes screening the human antigenicity potential of experimental human vaccines by testing them *in vitro* using defined human $CD4^+$and $CD8^+$ T cell clones, with T cell receptors that recognize epitopes on the experimental vaccines. The experimental vaccine can be used to pulse autologous or HLA matched human antigen presenting cells that will be recognized by specific $CD4^+$ or $CD8^+$ T cells and be quantitated by specific lysis of the antigen presenting cells or by proliferation of the human T cell clone or production of cytokines by the human T cell clone. Many vaccine constructs may be combined with various adjuvants. Therefore, the testing of multiple constructs and adjuvants at various doses could be accomplished quickly. The time and expense required for testing these experimental constructs can be reduced by the method of the invention because the promising vaccine constructs will be identified for subsequent development, based on the level of their ability to be processed and presented by human APC

and to be recognized *in vitro* by human T cell receptors. In addition, the *in vitro* assay could be used in dose response studies to measure the potency of various lots of vaccine.

While the prior art certainly teaches assays for T cell responses, the prior art does not teach the use of such an assay as a high through-put screen where each candidate shares a pre-defined T cell epitope and the T cells share a receptor specific for that epitope. Thus, the screen, rather than assaying for the presence or absence of the epitope in the vaccine composition, provides for a means for assessing the immunogenicity impact of other components in the vaccine composition.

Rejection of Claims 1-9 and 11-20 under 35 U.S.C. §103(a)

Claims 1-9 and 11-20 have been rejected under 35 U.S.C. §103(a) as unpatentable over Wisdom (Ed.) (Peptide Antigens ...), hereinafter "Wisdom", alone or in view of Zegers *et al.* (Immunological Recognition ...), hereinafter "Zegers *et al.*".

The Examiner maintains that Wisdom teaches the steps which could determine the minimum size of epitopes in peptides identified as containing epitopes, and that Wisdom, therefore, encompasses both screening for antigenic fragments which comprise T cell epitopes, and also screening for actual T cell epitopes within such fragments (Office Action, p. 2, lines 17-19). The Examiner asserts that the Claims are sufficiently broad to merely encompass the identification of one or more synthetic peptide fragments, or proteolytic fragments from among a collection of synthetic or proteolytic fragments as containing T cell epitopes (Office Action, p. 3, lines 1-5).

In response to this rejection, Claims 2-3, 9, 12-16 and 18-19 have been cancelled. Claims 1, 4-8, 11, 17, and 20 have been amended. Claims 21-22 have been added to better describe Applicant's invention.

Applicant's claims as amended screen vaccine compositions having a defined human T cell epitope, and therefore the claims do not include screening for T cell epitopes or identification of T cell epitopes. That is, it is known prior to the screen that each of the vaccines is characterized by the relevant epitope. The T cell response assessed by the claimed invention is specific for the defined human T cell epitope or defined peptide and known HLA allele for said T cell under conditions sufficient for said T cells to respond to the processed antigen. That is, it is known prior to the screen that the T cell has a receptor specific for the epitope. As a result of this specificity, Applicant's invention provides a method of rapid, relatively inexpensive *in vitro*

screening of great numbers of human vaccine candidates with known epitopes. It is a screen for the efficacy of the composition as a whole, not the epitope as such.

Applicant's panel of vaccine compositions must have or are known to express a defined human T cell epitope for monoclonal human T cell recognition. This is in distinct contrast to both Wisdom, which teaches that T cell epitopes can be identified by different screening assays (See p. 184, Figure 1, and p. 185, Table 1), and Zegers *et al.*, which teach the use of one or more proteolytic fragments, such as those obtained from a cathepsin D preparation, in a T cell proliferation assay to identify proteins containing T cell epitopes (See page 108, lines 26-51). The Examiner states that, "the purpose of the taught screening for T cell epitopes, in each reference, would have been **to identify** the peptides or fragments which contain T cell epitopes useful in a vaccine, following further testing of the identified peptide in animals/humans" (Office Action, p. 3 lines 5-12). Neither Wisdom nor Zegers *et al.* nor any of the prior art of record teaches or supports Applicant's method as claimed, to include screening a vaccine composition having or expressing a defined human T cell epitope for monoclonal human T cell recognition against a T cell having a receptor specific to the epitope. One of ordinary skill in the art would not be motivated to modify the reference to include a defined human T cell epitope in the vaccine, because the modification would destroy the intent, purpose and function of the teaching in the reference, *i.e.*, to identify the peptides or fragments which contain T cell epitopes.

Where the claimed invention is rejected as obvious, § 103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.* The court has further stated that:

> An obviousness rejection based upon the modification of a reference that destroys the intent, purpose and function of the teaching in the reference is not a proper obviousness rejection (*In re Gordon* 221 U.S.P.Q. 1125 (Fed, Cir. 1984)).

A person of skill in the art would not be interested in testing for what is already known to be present, and therefore would not be motivated to include a defined human T cell epitope in a vaccine according to Applicant's claimed method, in the method of Wisdom and/or Zegers *et al.*, because that would result in a modification of the reference "that destroys the intent, purpose and

function" of the Wisdom and/or Zegers *et al.* reference (for example, to identify the peptides or fragments which contain T cell epitopes).

Therefore, because the proposed combination and modification of prior art in an effort to attain the claimed invention destroys the intended function of the art, the requisite motivation would not have existed. The obviousness rejection is not proper (*In re Gordon* 221 U.S.P.Q. 1125 (Fed, Cir. 1984)).

Applicant's invention is novel and nonobvious over all the references of record. Applicant respectfully requests withdrawal of the rejection under U.S.C. §103(a). As amended, the claims relate to a method for determining the level of response of monoclonal human T cells, having a T cell receptor specific for a defined human T cell epitope, to the defined human T cell epitope when antigen presenting cells in culture are contacted with the epitope and subsequently, or simultaneously, contacted with human monoclonal T cells. The specification is enabling for the claimed method, as amended. Neither Wisdom nor Zegers *et al.* teaches or even suggests the use of human T cell clones that have defined specificity to evaluate the efficacy of vaccine compositions containing a defined human T cell epitope, and therefore, Applicant's claimed invention is both novel and nonobvious over the cited references.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Jacqueline M. Arendt

Jacqueline M. Arendt
Registration No. 43,474
Telephone (781) 861-6240
Facsimile (781) 861-9540

Lexington, Massachusetts 02421-4799
Dated: October 3, 2001

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

MARKED UP VERSION OF AMENDMENTS

1. (Twice Amended) A method for assessing the ability of a vaccine composition in a group consisting of two or more distinct vaccine compositions having a defined human T cell epitope or one or more nucleic acid molecules encoding one or more antigens which comprise said T cell epitope, to stimulate a monoclonal human T cell response, [wherein the vaccine composition comprises one or more antigens or one or more nucleic acid molecules encoding one or more antigens,] said method comprising the steps of:

(a) contacting human antigen presenting cells in culture with the vaccine composition, thereby, if said T cell epitope or one or more of the [antigens or] nucleic acid molecules are taken up and processed by [the] said antigen presenting cells, producing one or more processed antigens;

(b) contacting [the] said antigen presenting cells of step (a) with monoclonal human T cells having a T cell receptor specific for the defined human T cell epitope or defined peptide and known HLA allele for said T cells under conditions sufficient for [the] said T cells to respond to the processed antigen;

(c) determining [whether] the level of said T cells' response [T cells respond] to the processed antigen; and , if the vaccine composition exceeds a predetermined level of said T cells' response, [whereby, if the T cells respond to the processed antigen, the vaccine composition is capable of stimulating a T cell response; and
if the vaccine composition is capable of stimulating a T cell response, then]

(d) assessing the vaccine composition in one or more [animals or] human subjects.

4. (Amended) The method of Claim [2] 1 wherein the monoclonal human T cells are $CD8^+$ T cells and the T cell epitope is a CD8 epitope.

5. (Amended) The method of Claim [2] 1 wherein the monoclonal human T cells are $CD4^+$ T cells and the T cell epitope is a CD4 epitope.

6. (Amended) The method of Claim [2] 1 wherein the human antigen presenting cells are selected from the group consisting of macrophages, dendritic cells and B cells.

7. (Amended) The method of Claim [2] 1 wherein the level of human T cell response to the processed antigen is indicated by the release of one or more cytokines or lysis of the human antigen presenting cells.

8. (Amended) The method of Claim [3] 1 wherein the level of human T cell response to the processed antigen which is measured is the level of release of one or more cytokines or the level of stimulated formation of antibodies by B cells.

11. (Twice Amended) A method for selecting one or more vaccine compositions from among a group consisting of two or more vaccine compositions for assessment [in an animal or] in a human, said vaccine compositions each comprising a defined human T cell epitope [one or more antigens] or one or more nucleic acid molecules encoding one or more antigens which comprise said T cell epitope, said method comprising the steps of:

(a) contacting human antigen presenting cells in culture with a vaccine composition selected from among said group of vaccine compositions, thereby, if [one or more of the antigens] said T cell epitope or one or more of the nucleic acid molecules encoding one or more antigens which comprise said T cell epitope are taken up and processed by [the] said antigen presenting cells, producing one or more processed antigens;

(b) contacting [the] said antigen presenting cells of step (a) with monoclonal human T cells under conditions sufficient for [the] said T cells to respond to one or more of the processed antigens;

(c) determining [whether the T cells respond] the level of said T cells' response to one or more of the processed antigens; [whereby if the T cells respond to one or more of the processed antigens, then the vaccine composition stimulates a T cell response;]

(d) repeating steps (a), (b) and (c) with each additional vaccine composition in the group[, thereby determining whether each vaccine composition stimulates a T cell response]; and[,

if one or more of the vaccine compositions stimulates a T cell response]

(e) selecting at least one vaccine composition <u>that exceeds a predetermined level of said T cells' response</u> [which stimulates a T cell response] for assessment in one or more [animals or] human subjects.

17. (Twice Amended) The method of Claim [16] <u>11</u> wherein the monoclonal <u>human</u> T cells are $CD8^+$ T cells or $CD4^+$ T cells <u>and the T cell epitope is a CD8 epitope or CD4 epitope.</u>

20. (Twice Amended) The method of Claim [~~18~~] <u>11</u> wherein the <u>human</u> antigen presenting cells are autologous cells with the monoclonal T cells.